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Straightforward Synthesis of α,ß-Unsaturated Acids and Derivatives

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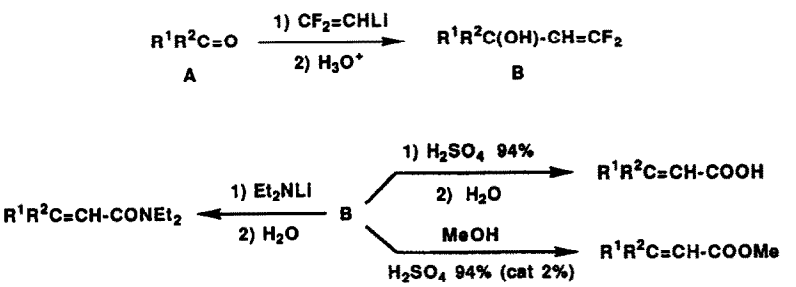
Abstract: *A general C_2 vinylic homologation from carbonyl compounds (aldehydes or ketones) which leads to various α,ß-insaturated acids, esters and amides, is described.*

α,ß-Unsaturated acids and derivatives are well recognized as useful building blocks in organic synthesis and various methods to prepare them are published. Recent publications[1] report the known methods that allow to reach such compounds with the predominant *E* geometry.

Herein, we report a general, straightforward synthesis of such 2-alkenoic acids and derivatives starting from various carbonyl compounds. Our procedure is based upon two keys steps. An initial reaction between 2,2-difluorovinyl lithium, prepared *in situ* with 1,1-difluoroethylene and s-BuLi, and carbonyl compounds **A** leads to ß,ß-difluorinated allylic alcohols **B** for which we have previously described the preparation[2]. Secondly, the intermediate alcohols **B** can undergo an allylic rearrangement in acidic medium to afford the corresponding acid derivatives, and a nucleophilic attack in basic medium to afford amides.



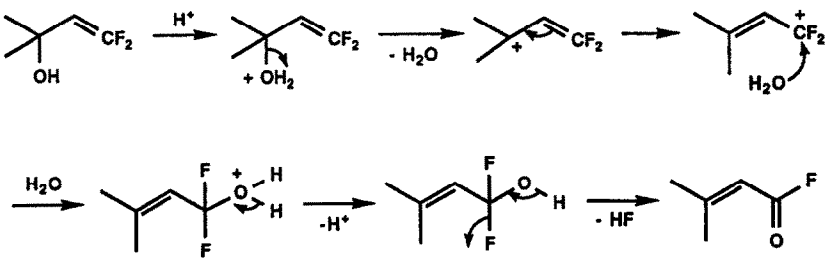
$$R^1R^2C{=}O \xrightarrow[2)\ H_3O^+]{1)\ CF_2{=}CHLi} R^1R^2C(OH){-}CH{=}CF_2 \xrightarrow[or\ Et_2NLi]{H_3O^+\ or\ MeOH} R^1R^2C{=}CH{-}COZ\ (Z = OH,\ OCH_3,\ NEt_2)$$

R^1	R^2	Products	Configuration[a]	Yield (%)	b.p. or m.p.
n-Pr	H	Pr-CH=CH-COOH **1**	E	60	m.p. 32-33°
Ph	CH_3	Ph-C(CH_3)=CH-COOH **2**	E	80	m.p. 95-97°
(Z)-n-Pr-CH=CF	H	Pr-CH=CF-CH=CH-COOH **3**	E,Z	75	decomp.
$(CH_2)_5$		$(CH_2)_5$C=CH-$COOCH_3$ **4**	--	67	b.p. 42°/0.01
Thienyl	H	Th-CH=CH-$COOCH_3$ **5**	E	80	m.p. 50-51°
n-Pent-C≡C	H	Pent-C≡C-CH=CH-$COOCH_3$ **6**	E/Z=85/15	75	*b
(E,E)-Me-$(CH{=}CH)_2$	H	Me-$(CH{=}CH)_3$-$COOCH_3$ **7**	E,E,E	70	m.p. 75°
n-Pr	H	Pr-CH=CH-$CONEt_2$ **8**	E	70	**b
(E)-n-Pent-CH=CH	H	Pent-$(CH{=}CH)_2$-$CONEt_2$ **9**	E,E	67	**b

a: E/Z ratio determined by ^1H NMR

b: products are purified by flash silica-gel chromatography (cyclohexane/EtOAc=80/20* or 50/50**).

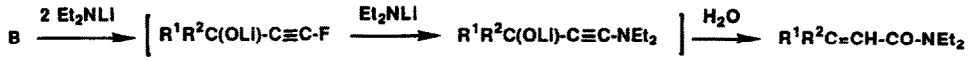
When the alcohols **B** are treated by a sulfuric acid solution (94%), they undergo rapid allylic migration to give the intermediate acid fluorides.



In such acidic conditions, these intermediate acid fluorides, which are not very stable compounds, cannot be isolated. They lead rise in presence of water or alcohols to the corresponding α,ß-unsaturated acids or esters respectively.

On the other hand, in basic medium, the treatment of alcohols **B** by lithium amide, affords amides. Three equivalents of lithium amide are necessary: i) metalation of alcohol; ii) elimination of HF to led to a fluoroalkyne; iii) substitution of a fluorine atom by an amino group[3] according to an addition-elimination mechanism to afford an ynaminol.

The action of lithium diethylamide on 1,1-difluoroalkenes is a convenient route to ynamines[4]. In our case, the intermediate ynaminol is transformed into α,ß-ethylenic amide[5].



This synthesis possesses several advantages: a wide variety of aliphatic and aromatic carbonyl compounds, aldehydes but also ketones, are commercially available, and CF_2=CHLi is readily prepared and used *in situ*. The reaction (two steps) is convenient and very fast to carry out: alcohols **B** is used crude without further purification and gives directly acid, ester or amide.

This reaction is stereoselective (if R^2=H or if R^1=Ph and R^2=Me, only one isomer is obtained, having the *E* configuration; in the case of the enynic compound **6**, the two isomers are obtained (E/Z=85/15), due to the isomerisation of the intermediate carbocation before the nucleophilic attack) and regioselective (in the case of polyinsaturated carbonyl compounds, several migrations are possible in acidic medium, but only the irreversible formation of α,ß-unsaturated acid fluoride is observed, due to the stability of fluorocarbocation).

Experimental procedure: the treatment of carbonyl derivatives **A** with 2,2-difluorovinyl lithium, prepared *in situ* from 1,1-difluoroethylene and s-BuLi in THF and Et_2O (80/20) at -100°C (15 min), leads to the difluorinated alcohols **B**. The latter are unstable and must be used crude. To obtain: i) the acid: the alcohol **B** (20 mmol) is added at -15°C to a stirred solution of 94% sulfuric acid (30 ml) (10 min). The mixture is poured on to crushed ice and then extracted with Et_2O; ii) the ester: the alcohol **B** (20 mmol) is added at 20°C to a stirred solution of CH_3OH (30 ml) and 94% sulfuric acid (0.5 ml) (2 h); iii) the amide: the alcohol **B** (20 mmol) is added at -70°C to a solution of Et_2NLi/THF (70 mmol). Stirring is continued for 1 h at 20°C. The products are purified by distillation (**4**), recrystallisation from hexane (**1,2,3,5,7**) or flash silica-gel chromatography (**6,8,9**). As all intermediate alcohols **B** are unstable, all yields are based on the starting carbonyl compounds **A**.

In conclusion, this route appears to be a general and highly regioselective methodology for the introduction of acid, ester and amide function in various insaturated systems (alkenes, styrenes, dienes, trienes); this reaction allowed us to prepare readily products[6] of high stereoisomeric and chemical purities, in good overall yields and in two steps from available starting materials.

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References and notes

1. For the recent examples: Outurquin, F. ; Paulmier, C. *Synthesis* **1989**, *9*, 690-691 and references cited therein; Patois, C. ; Savignac, P. *Tetrahedron Lett.* **1991**, *32*, 1317-1320; Godfrey, A.G. ; Ganem, B. *Tetrahedron Lett.* **1992**, *33*, 7461-7464; Coutrot, P. ; Grison, C. ; Gérardin-Charbonnier, C. ; Lecouvey, M. *Tetrahedron Lett.* **1993**, *34*, 2767-2770.

2. Sauvêtre, R. ; Normant, J.F. *Tetrahedron Lett.* **1981**, *22*, 957-958.

3. Sauvêtre, R. ; Normant, J.F. *Tetrahedron Lett.* **1982**, *23*, 4325-4328.

4. Strobach, D.R. *J. Org. Chem.*, **1971**, *36*, 1438-1440.

5. Ficini, J. ; Barbara, C. ; Dureault, A. *C. R. Acad. Sci. Paris* **1967**, *265*, 1496-1498.

6. The products described therein were characterized *via* their spectroscopic properties. Infrared spectra were measured on a Perkin-Elmer 397 spectrometer (neat,cm^{-1}) and ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR 300 spectrometer($CDCl_3$, δ(ppm) from TMS, J(Hz)).

2: IR: 1680, 1620, 1270, 1210; ^{1}H NMR: 2.61 (d,3H), 6.18 (d,1H) J=1.3, 7.38-7.51 (m,5H), 10.40 (s,1H); ^{13}C NMR: 18.3, 116.5, 126.5, 128.6, 129.4, 142.1, 158.6, 172.5.

3: IR: 1685, 1645, 1620; ^{1}H NMR: 0.94 (t,3H), 1.47 (hex,2H), 2.24 (q,2H), 5.29 (dt,H^5), 6.08 (d,H^2), 7.10 (dd,H^3), JH^5F=34.6, JH^3F=26.6, JH^2H^3=15.5, JH^5H^6=7.8, 11.4 (s,1H); ^{19}F NMR (Jeol FX 90, $CDCl_3$, δ(ppm) from $PhCF_3$, J(Hz)): -61.4 (dd), JFH^5=34.6, JFH^3=26.6; ^{13}C NMR: 13.7, 22.1, 26.8, 116.6 (s,C^2), 121.0 (d,C^5) J=15.7, 138.2 (d,C^3) J=24.1, 155.1 (d,C^4) J=248.8, 172.2 (s,C^1).

6: IR: 2200, 1720, 1610, 1300, 1150; ^{1}H NMR: 0.9 (t,3H), 1.35 (m,4H), 1.55 (m,2H), 2.37 (td,2H), 3.75 (s,3H), 6.15 (d,H^2), 6.77 (dt,H^3), JH^2H^3=15.8, JH^3H^6=2.3; ^{13}C NMR: 14.0, 19.8, 22.2, 28.1, 31.1, 51.8, 78.0, 101.1, 126.5, 128.8, 166.7.

7: IR: 1715, 1610, 1265, 1130, 1000; ^{1}H NMR: 1.83 (d,3H), 3.74 (s,3H), 5.84 (d,H^2), 5.94 (dq,H^7), 6.15 (ddq,H^6), 6.20 (ddq,H^4), 6.52 (dd,H^5), 7.30 (dd,H^3), JH^2H^3=15.3, JH^6H^7=15.0, JH^4H^5=14.8, JH^3H^4=11.3, JH^5H^6=10.9, JH^7H^8=6.8, JH^6H^8=1.6, JH^4H^8=0.6; ^{13}C NMR: 18.6, 51.5, 119.6, 127.6, 131.2, 135.3, 141.3, 145.2, 167.7.

9: IR: 1645, 1620, 1595, 1420, 1260, 1125, 995; ^{1}H NMR: 0.89 (t,3H), 1.15 (t,3H), 1.20 (t,3H), 1.29 (m,4H), 1.41 (m,2H), 2.15 (q,2H), 3.38 (q,2H), 3.44 (q,2H), 6.06 (dt,H^5), 6.19 (d,H^2), 6.20 (dd,H^4), 7.29 (dd,H^3), JH^4H^5=15.1, JH^2H^3=14.8, JH^3H^4=10.7, JH^5H^6=6.8; ^{13}C NMR: 13.2, 14.0, 15.0, 22.5, 28.5, 31.4, 32.9, 40.9, 42.2, 118.7, 128.9, 142.86, 142.94, 166.2.

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